



**Karolinska
Institutet**

**Övre gastrointestinal forskning
Institutionen för molekylär medicin och kirurgi
Karolinska Institutet**

Risk factors and prevention of esophageal cancer

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Karolinska
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av

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Abstract

Esophageal cancer is the eighth most common cancer in the world, consisting of two major histological types: squamous cell carcinoma (dominant globally) and adenocarcinoma (rapidly increasing in incidence in the Western world during the last decades). Established risk factors for adenocarcinoma are gastroesophageal reflux symptoms, obesity and tobacco smoking, whereas squamous cell carcinoma is mainly associated with tobacco smoking and excessive alcohol intake. Esophageal cancer predominantly affects men; the gender difference in squamous cell carcinoma cases is entirely explained by the higher prevalence of risk factors in men, but the striking 7:1 sex ratio in adenocarcinoma remains unexplained. Esophageal cancer carries a very poor prognosis and despite efforts to improve survival the overall 5-year survival rate is still less than 10%, emphasizing the need for preventive factors. This thesis focuses on the etiology of esophageal cancer and the unexplained male predominance in esophageal adenocarcinoma.

The first paper investigates differences in risk factor profiles between women and men as a possible explanation for the male predominance in esophageal and cardiac adenocarcinoma. The paper was based on a nationwide population-based case-control study of all newly diagnosed cases of adenocarcinoma (n=451) and corresponding controls (n=816) in Sweden between 1994-1997. Contradictory to the hypothesis, the point odds ratios (OR) did not indicate any weaker association of the established risk factors reflux, obesity and tobacco smoking with risk of esophageal adenocarcinoma in women (4.6, 10.3, and 5.3, respectively) compared to men (3.4, 5.4, and 2.8, respectively). Protective factors such as a high intake of fruit and vegetables or infection with *Helicobacter pylori* showed no stronger protective effect in women. Thus, gender differences in the exposure to known risk factors do not seem to explain the male predominance in esophageal or cardiac adenocarcinoma.

The second paper investigated if the higher incidence rate of esophageal adenocarcinoma in the United Kingdom compared to Sweden is explained by a higher population prevalence of established risk factors. Investigations were based on identical questionnaires filled out by a random sample of the English (n=3633) and Swedish (n=1483) populations. The prevalence of gastroesophageal reflux symptoms and obesity were significantly higher in the English population (OR 2.0, 95% CI 1.6-2.4 and OR 1.8, 95% CI 1.5-2.1), suggesting that the higher incidence of esophageal adenocarcinoma in the United Kingdom is at least partly due to the higher population prevalence of well-established risk factors.

The third paper investigates why surgical intervention of reflux does not provide protection against esophageal adenocarcinoma. All esophageal or cardiac adenocarcinoma cases among antireflux operated patients in Sweden in 1965-2006 were identified and compared with matched controls from the same antireflux cohort. Recurrence of reflux after surgery was a risk factor for esophageal adenocarcinoma (OR 3.1, 95% CI 1.5-6.3), while BMI, tobacco smoking and type of antireflux surgery appeared to be of lesser importance. Recurrent reflux can explain the lack of a cancer protective effect of antireflux surgery and endoscopic surveillance might be an option for these patients.

The fourth paper investigates the association between infection with human papillomavirus (HPV) and tumor location in the esophagus. The hypothesis is based on an oral route of transmission and an association between HPV and oropharyngeal squamous cell carcinoma. Available tumor material from esophageal squamous cell carcinomas in the Stockholm County in 1999-2006 was collected and examined for presence of HPV using multiplex polymerase chain reaction (PCR) with Luminex. No increased occurrence of HPV DNA was observed in esophageal squamous cell carcinomas located in the proximal compared to a more distal part of the esophagus. The prevalence of HPV DNA (10%) was low, and the identified HPV did not seem to be biologically active, based on p16^{INK4a} data.